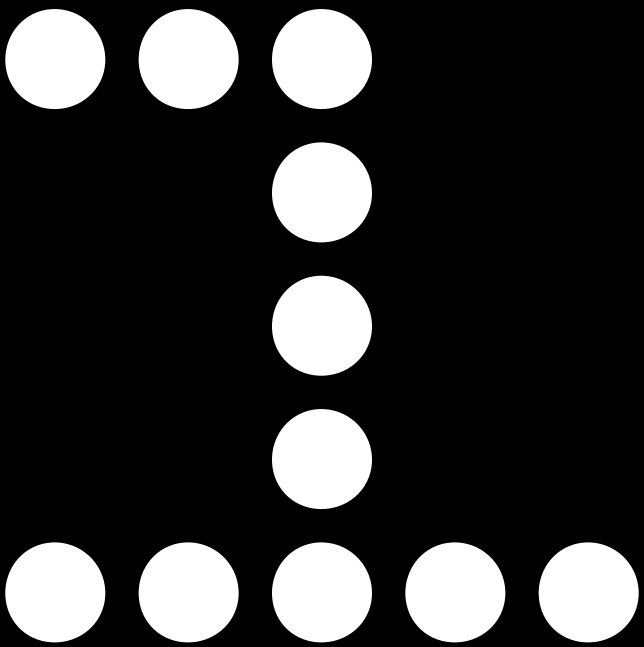

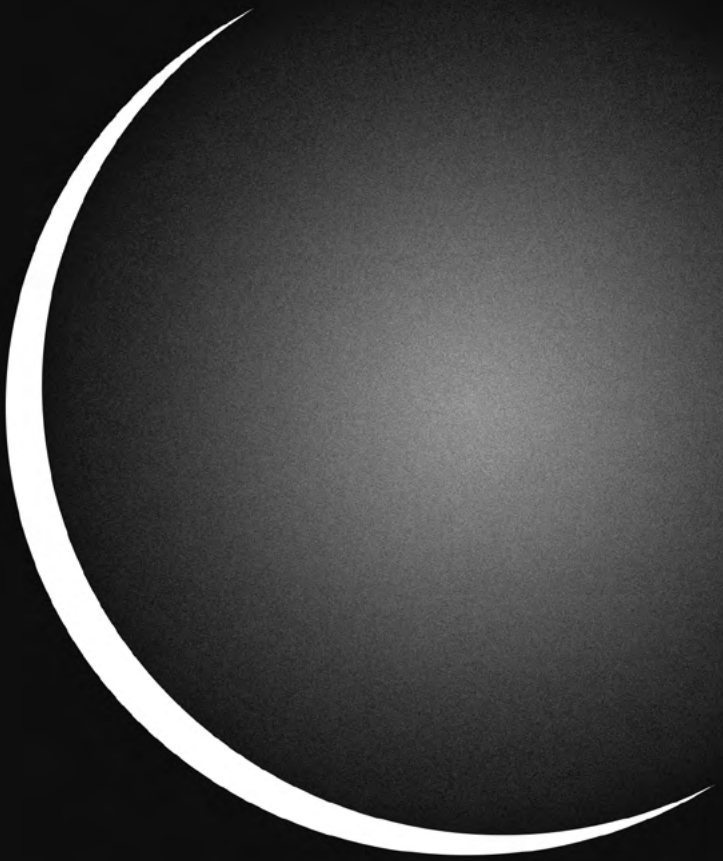

GENERAL INTRODUCTION

For a human being, vision is presumably the most important of the physical senses to perform daily activities. Loss of vision limits participation in society and decreases quality of life.[1–3] Eye diseases like glaucoma are more common in the elderly; a population that will almost double the upcoming decades.[4] Therefore, investing in the study of eye diseases and the interaction of ophthalmic patients with their environment is essential.

This general introduction will provide you with the background information to appreciate how the two main themes of this thesis - glaucoma and light - come together in the main objective of this thesis. First, **glaucoma** as an eye disease will be introduced. Second, some day-to-day examples will provide context for the **physical quantities of light** used in the experiments. Third, the physiology of **light and dark adaptation** gives some basic insight on how the visual sensitivity remains optimal under different light conditions. Fourth, **contrast sensitivity** as a measure to quantify visual sensitivity will be discussed. Finally, the available knowledge on the visual function of **glaucoma patients under extreme luminances** will serve as a prelude to the **aims and outline of this thesis**.

GLAUCOMA

Vision starts with light that passes through the cornea, the pupil, the lens, the vitreous body, and eventually reaches the retina. Photoreceptors in the retina convert light into an electric signal that is transferred through the optic nerve to the brain. After the signal is processed and interpreted, our brain forms the image we see of the outside world. Glaucoma is a chronic and progressive eye disease in which the optic nerve is damaged. This is characterized by the loss of retinal ganglion cells (RGCs) and thinning of the retinal nerve fiber layer (RNFL). Consequently, the visual field is damaged, typically starting in the periphery.[5] There are different forms of glaucoma, of which the most common form in Caucasians is Primary Open Angle Glaucoma (POAG).[6] As the research performed in this thesis primarily concerns patients with POAG, POAG from this point on will be referred to as 'glaucoma'. Glaucoma has a prevalence of 2% and is the leading cause of irreversible blindness in the world.[7] The most important risk factor for glaucoma is an increased intraocular pressure; the combination with a suspicious-appearing optic nerve and an abnormal visual field establishes the diagnosis.[8] Other risk factors include older age, myopia, and a positive family history for glaucoma.[9,10] Decreasing the intraocular pressure is the only effective treatment currently available.[11,12] Glaucoma follow-up consists of the measurement of the intraocular pressure, and the assessment of the optical nerve head, the visual field (perimetry), and the RNFL.[8]

The early detection of glaucoma is crucial, as damage to the optic nerve and the subsequent visual field cannot be undone. However, the disease course is insidious, leading to a delay between the onset and the diagnosis of glaucoma. This is a consequence of the inability of patients to physically perceive high intraocular pressure, which would have urged them to go to an ophthalmologist. In addition, visual field loss in one eye can be compensated for by information from the other eye, and masked by the brain's ability to 'fill in' the damaged parts of the visual field.[13] Therefore, glaucoma

patients are considered to be asymptomatic, and often unaware of their disease until at a late stage.[5] However, patients may have been experiencing visual symptoms at an early stage that we did not yet recognize as related to glaucoma. *In the ophthalmology outpatient clinic, glaucoma patients themselves spontaneously reported poor vision under low, high, and changing light conditions as symptom. Therefore, the study to the influence of light conditions on visual functioning in glaucoma, which will be described in this thesis, was a logical step.*

PHYSICAL QUANTITIES OF LIGHT

To appreciate what low and high light conditions are, some knowledge regarding the physical quantities used to describe the amount of light is necessary. The visible part of the electromagnetic spectrum is called light. On the box of a light bulb, the amount of light reported is in lumens. Especially with the traditional incandescent bulb, a significant amount of power consumed (i.e., energy per time expressed in Watts, or Joules per second) is converted into heat. The amount of power that is converted into light is expressed in lumens (lm), which is the unit of luminous flux. The luminous flux that is incident on a surface of one square meter is called illuminance, which is expressed in lux (lm/m^2). Although these physical quantities are indicative for the amount of light, the luminous flux and illuminance are not what we perceive. What we perceive is the amount of illuminance that is reflected by a surface: the luminance in candela per square meter (cd/m^2). In the case of a perfectly diffusely reflecting surface (Lambertian reflectance), the luminance can be calculated by dividing the illuminance by π (Lambert's cosine law). Because light is also partially absorbed by a surface, the resulting value is multiplied by a reflection factor (reflectance). The advantage of using luminance as the physical quantity of light, is that it is independent of the distance. Finally, the actual amount of light on our retina is influenced by pupil size. Therefore, the luminance is multiplied by the pupil area in square millimeter to obtain the retinal illuminance in Troland (Td).

In the experiments of this thesis, we mainly focus on the luminance as the physical quantity of light. To give an idea of luminances in daily life: a white paper under starlight has a luminance of $\sim$0.001 cd/m^2, under moonlight $\sim$0.01 cd/m^2, under indoor lighting $\sim$100 cd/m^2, and under sunlight $\sim$10,000 cd/m^2. Some possibly more applicable examples from 21st century daily life: the luminance of a white text document on a computer screen is usually $\sim$150 cd/m^2, and the luminance of a white screen of a 2.5 year old iPhone 5s can be adjusted from $\sim$3 to $\sim$350 cd/m^2.

LIGHT AND DARK ADAPTATION

Light and dark adaptation allows the visual sensitivity to remain optimal over a wide range of luminances.[14] Since the luminance under starlight is about 10^7 times lower than the luminance under sunlight, adaptation is a crucial prerequisite for vision in daily life.[15–17] While pupil size and neural adaptation have a modest role, the most important factor in adaptation is based on photochemistry in photoreceptors (cones and rods). Photoreceptors contain light-sensitive and light-insensitive photopigment.

When adapted to high luminances, a large amount of the photopigment is reduced to the light-insensitive form ('bleaching'). The reduced concentration of light-sensitive photopigment in the cones and rods leads to a reduced sensitivity of the eye to light. When adapted to low luminances, the light-sensitive photopigment is regenerated which – consequently – increases the sensitivity of the eye to light.[18] Rods are more sensitive to light than cones; unlike cones, rods will be completely completely depleted of light-sensitive photopigment ('bleached') at high luminances. Therefore, only cones are responsible for photopic vision (>3 cd/m^2), both cones and rods for mesopic vision (0.03-3 cd/m^2), and only rods for scotopic vision (<0.03 cd/m^2).[19] Although rods are more sensitive to light, the chemical regeneration of photopigment occurs four times as slow compared to the pigment in cones. The implication of the sensitivity and recovery speed of cones and rods come together in the dark adaptation curve (Fig. 1), which shows the sensitivity of the eye as a function of time after exposure to an extremely high luminance. The initial, rapid increase in sensitivity is caused by dark adaptation of the cones. After this cone adaptation, rods catch up and achieve a much higher sensitivity. The solid line represents the resulting retinal sensitivity of both cones and rods. The dark adaptation curve explains why we almost immediately see something when going into the dark, but need more time to fully employ our visual sensitivity.

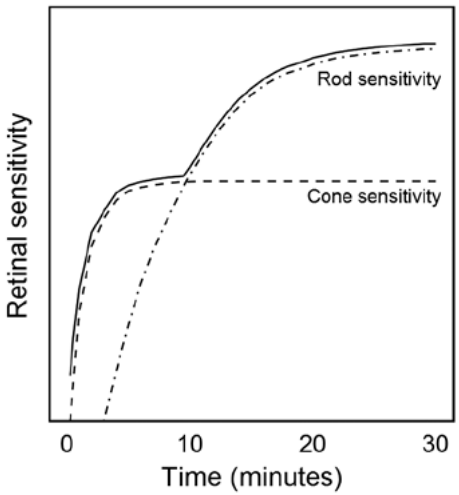

Figure 1. *Retinal sensitivity as a function of time after exposure to an extremely high luminance (i.e., the dark adaptation curve). The initial, rapid increase in sensitivity is caused by dark adaptation of the cones. After this cone adaptation, the rods catch up and achieve a much higher sensitivity. The solid line represents the resulting retinal sensitivity of both cones and rods.*

CONTRAST SENSITIVITY

A common method to quantify visual sensitivity is by means of the contrast sensitivity. Contrast sensitivity (CS) is defined as the smallest luminance difference that a visual system is able to detect. Luminance differences are described by means of contrast. Contrast can be calculated in two ways: (1) contrast for small stimuli on large uniform

backgrounds (Weber contrast; see the front cover of this thesis), and (2) contrast for gratings (Michelson contrast; Fig. 2). In the experiments of this thesis, both Weber and Michelson contrast will be used. The CS is the reciprocal of the smallest detectable contrast (the threshold contrast). In formula:

(1) Weber contrast: $\frac{L_s - L_b}{L_b}$

(2) Michelson contrast: $\frac{L_{max} - L_{min}}{L_{max} + L_{min}}$

Contrast sensitivity: $\frac{1}{|\ treshold\ contrast\ |}$

where L_s is the luminance of the stimulus, L_b the luminance of the background, L_{max} and L_{min} the maximum and minimum luminance within the grating. The CS is commonly reported as the logarithm to base 10 of the CS: the logCS.

CONTRAST SENSITIVITY & SPATIAL FREQUENCY

The CS is dependent on the spatial characteristics of stimuli, which can be assessed by using gratings of different widths. The width of a grating can be described by the spatial frequency: the number of cycles (black and white bars) per degree of visual angle (cpd). To illustrate, one degree of visual angle subtends approximately the width of the index fingernail at arm's length. A low spatial frequency (e.g., 1 cpd) means broad bars, whereas a high spatial frequency (e.g., 10 cpd) means thin bars (Fig. 2).

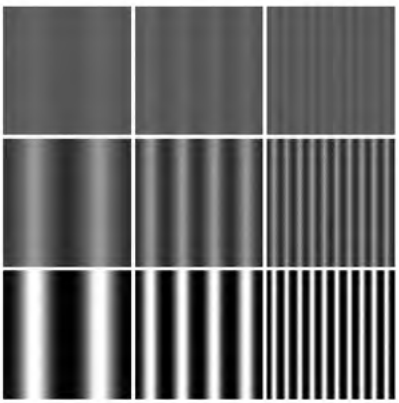

Figure 2. *Vertically oriented sine-wave gratings. Spatial frequency increases from left to right. Contrast increases from top to bottom.*

The logCS as a function of spatial frequency is called the contrast sensitivity function (CSF; Fig. 3). The maximum of the CSF is caused by processing of visual information by the RGCs, called lateral inhibition. Lateral inhibition starts with the area on the retina over which the firing rate of an RGC is influenced: the receptive field. Light that falls only on the center of the receptive field increases the firing rate; light that falls only

on the surround decreases it. When light falls on both the center and the surround, the excitation from the center is inhibited by the surround, and the firing rate remains unchanged.[15] Because of lateral inhibition, the human retina is the most sensitive to gratings that excite only the center of the receptive field. At high luminances, this occurs around a spatial frequency of 3-4 cpd.[20] Towards lower and higher spatial frequencies, the CS decreases because light falls on both the excitatory center and inhibitory surround of the receptive field. At higher spatial frequencies, the logCS decreases even further because of the acuity limits of the visual system.[15]

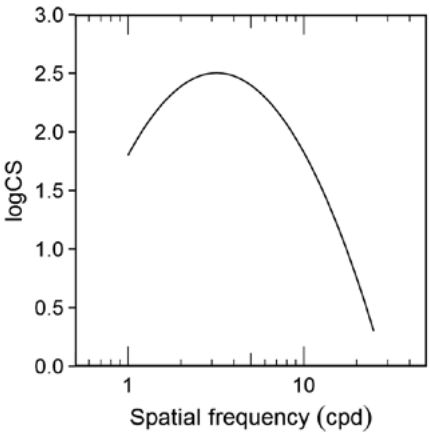

Figure 3. *The logCS as a function of spatial frequency (i.e., the contrast sensitivity function). The maximum of the CSF at 3-4 cpd is caused by lateral inhibition (see text). Towards lower and higher spatial frequencies, the CS decreases because of reduced lateral inhibition. At higher spatial frequencies, the logCS decreases even further because of the acuity limits of the visual system.*

CONTRAST SENSITIVITY & LUMINANCE

In addition to its dependence on the spatial frequency, the CS is also influenced by the luminance condition under which it is measured. The CS as a function of spatial frequency and luminance in healthy subjects is established by the research field that studies the relation between stimulus and perception, so called psychophysics. When measuring the CS at different luminances, two major psychophysical laws are applicable (Fig. 4):

(1) the De Vries-Rose law: the CS is proportional to the square root of the luminance at low luminances.[21,22]

(2) Weber's law: the CS is constant at high luminances.[23]

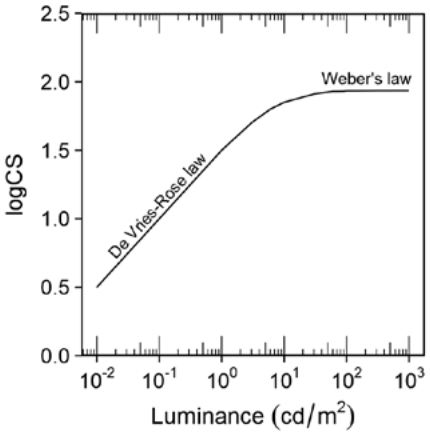

Figure 4. *The logCS as a function of luminance. At low luminances, the CS is proportional to the square root of the luminance (the De Vries-Rose law). At high luminances, the CS is constant (Weber's law).*

GLAUCOMA PATIENTS UNDER EXTREME LUMINANCES

To summarize, glaucoma is characterized by the loss of RGCs and visual field defects, the wide range of luminances in daily life are processed by adaptation, and the CS can be used to quantify visual sensitivity. What is there still to unravel?

1. Subjective visual function
Although glaucoma patients are considered to be asymptomatic, fragmentary findings revealed that they seem to experience visual difficulties under extreme (low, high, or rapidly changing) luminance conditions.[24–29] This might suggest an impaired light and dark adaptation, which would be an intriguing finding, because the cones and rods – rather than the RGCs – are thought to be the primary site of adaptation.

2. Objective visual function
It is generally accepted that glaucoma patients have a lower CS compared to healthy subjects.[30–39] However, previous studies that included glaucoma patients measured the visual function only at one comfortable luminance condition, and not towards the extremes. If the difference between glaucoma patients and healthy subjects in extreme luminances is indeed more pronounced, this may be helpful for improving diagnostic tests and commencing treatment earlier.

AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to unravel the effect of luminance on visual functioning in glaucoma patients. We specified our objective into two primary aims:

(1) To determine the effect of luminance on **subjective** visual functioning in glaucoma.
(2) To determine the effect of luminance on **objective** visual functioning in glaucoma.

Apart from influencing visual responses to light, glaucoma might also influence nonvisual responses to light, such as the sleep-wake cycle. In healthy subjects, the circadian clock is entrained to light by the input of a special type of RGCs: the intrinsically photosensitive RGCs (ipRGCs). Loss of ipRGCs in glaucoma patients might result in a lower susceptibility of the circadian clock to light and a change in the sleep-wake cycle. Therefore, we explore the influence of glaucoma on the chronotype (the midpoint between sleep onset and wake-up time on days off), which is a marker for the circadian phase.

This thesis focuses primarily on the difference in visual functioning between glaucoma patients and healthy subjects. Therefore, all projects – except for the citizen science project in Chapter 6 – included a group of glaucoma patients and controls. In **Chapter 2**, a newly developed questionnaire is used to determine the effect of luminance on subjective visual functioning. **Chapter 3** describes the applicability of the above mentioned psychophysical laws. In **Chapter 4**, the visual function from star- to sunlight is objectified by means of the contrast sensitivity at different spatial frequencies. **Chapter 5** describes the results of the traditional light and dark adaptation experiment. In **Chapter 6**, a citizen science network of smartphone users provides information about the relation between visual complaints and luminances from real-life environments after dark. **Chapter 7** focuses on the chronotype. Finally, the summary and general discussion in **Chapter 8** summarizes the most important findings, connects subjective to objective visual functioning of glaucoma patients at different luminances, discusses the clinical implications of our findings, and provides recommendations for future research.

REFERENCES

1. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol*. 2000;118(1):47-51.

2. van Gestel A, Webers CAB, Beckers HJM, et al. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* . 2010;24(12):1759-1769.

3. Goldberg I, Clement CI, Chiang TH, et al. Assessing quality of life in patients with glaucoma using the Glaucoma Quality of Life-15 (GQL-15) questionnaire. *J Glaucoma.* 2009;18(1):6-12.

4. Stoeldraijer L, Van Duin C, Huisman C. *Bevolkingstrends Kernprognose 2016–2060: 18 miljoen inwoners in 2034 voorzien.* CBS; 2010.

5. Duke-Elder *S. System of Ophthalmology: Diseases of the Lens and Vitreous: Glaucoma and Hypotony.* St. Louis: CV Mosby; 1969:443-477.

6. Klaver CC, Wolfs RC, Vingerling JR, Hofman A, de Jong PT. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch Ophthalmol.* 1998;116(5):653-658.

7. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences - The Rotterdam Study. *Invest Ophthalmol Vis Sci.* 2000;41(11):3309-3321.

8. European Glaucoma Society. Terminology and guidelines for glaucoma. http://bjo.bmj.com/content/bjophthalmol/101/4/1.full.pdf. Published June 2014. Accessed October 20, 2017.

9. Springelkamp H, Wolfs RC, Ramdas WD, et al. Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. *Eur J Epidemiol.* June 2017. doi:10.1007/s10654-017-0270-y.

10. Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology.* 2011;118(10):1989-1994.e2.

11. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268-1279.

12. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120(6):701-713; discussion 829-830.

13. Hoste AM. New insights into the subjective perception of visual field defects. *Bull Soc Belge Ophtalmol.* 2003;(287):65-71.

14. Zihl J, Kerkhoff G. Foveal photopic and scotopic adaptation in patients with brain damage. *Clinical Vision Sciences.* 1990;5(2):185-195.

15. Snowden R, Thompson P, Troscianko T. *Basic Vision: An Introduction to Visual Perception.* Oxford University Press; 2012.

16. Rushton WAH. The Ferrier Lecture, 1962: Visual adaptation. *Proceedings of the Royal Society B: Biological Sciences.* 1965;162(986):20-46.

17. Hood DC, Finkelstein MA. Sensitivity to light. In: Boff K, Kaufman L, Thomas J, eds. *Handbook of Perception and Human Performance.* New York: John Wiley and Sons; 1986:5.1-5.62.

18. Guyton AC, Hall JE. *Textbook of Medical Physiology.* W B Saunders Company; 2006:626-639.

19. Atchison DA, Smith G. *Optics of the Human Eye.* Edinburgh: Butterworth-Heinemann; 2002:101.

20. Campbell FW, Robson JG. Application of Fourier analysis to the visibility of gratings. *J Physiol.* 1968;197(3):551-566.

21. Rose A. The sensitivity performance of the human eye on an absolute scale. *J Opt Soc Am.* 1948;38(2):196-208.

22. de Vries HL. The quantum character of light and its bearing upon threshold of vision: the differential sensitivity and visual acuity of the eye. *Physica.* 1943;10(7):553-564.

23. Duke-Elder S. *The Physiology of the Eye and of Vision.* St. Louis: CV Mosby; 1968:583.

24. Lee BL, Gutierrez P, Gordon M, et al. The Glaucoma Symptom Scale. A brief index of glaucoma-specific symptoms. *Arch Ophthalmol.* 1998;116(7):861-866.

25. Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE. Quality of life in newly diagnosed glaucoma patients: the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology.* 2001-1;108(5):887-898.

26. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol.* 1999;83(5):546-552.

27. Janz NK, Wren PA, Lichter PR, et al. The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology.* 2001-2;108(11):1954-1965.

28. Hu CX, Zangalli C, Hsieh M, et al. What do patients with glaucoma see? Visual symptoms reported by patients with glaucoma. *Am J Med Sci.* 2014;348(5):403-409.

29. Tatemichi M, Nakano T, Hayashi T, et al. Symptoms related to glaucomatous visual field abnormalities among male Japanese workers in a population-based setting. *Acta Ophthalmol.* 2012;90(6):546-551.

30. Adams AJ, Heron G, Husted R. Clinical measures of central vision function in glaucoma and ocular hypertension. *Arch Ophthalmol.* 1987;105(6):782-787.

31. Onal S, Yenice O, Cakir S, Temel A. FACT contrast sensitivity as a diagnostic tool in glaucoma: FACT contrast sensitivity in glaucoma. *Int Ophthalmol.* 2008;28(6):407-412.

32. Ansari EA, Morgan JE, Snowden RJ. Psychophysical characterisation of early functional loss in glaucoma and ocular hypertension. *Br J Ophthalmol.* 2002;86(10):1131-1135.

33. Horn F, Martus P, Korth M. Comparison of temporal and spatiotemporal contrast-sensitivity tests in normal subjects and glaucoma patients. *Ger J Ophthalmol.* 1995;4(2):97-102.

34. Arden GB, Jacobson JJ. A simple grating test for contrast sensitivity: preliminary results indicate value in screening for glaucoma. *Invest Ophthalmol Vis Sci.* 1978;17(1):23-32.

35. Ross JE, Bron AJ, Clarke DD. Contrast sensitivity and visual disability in chronic simple glaucoma. *Br J Ophthalmol.* 1984;68(11):821-827.

36. Vaegan, Halliday BL. A forced-choice test improves clinical contrast sensitivity testing. *Br J Ophthalmol.* 1982;66(8):477-491.

37. Wood JM, Lovie-Kitchin JE. Evaluation of the efficacy of contrast sensitivity measures for the detection of early primary open-angle glaucoma. *Optom Vis Sci.* 1992;69(3):175-181.

38. Sample PA, Juang PS, Weinreb RN. Isolating the effects of primary open-angle glaucoma on the contrast sensitivity function. *Am J Ophthalmol.* 1991;112(3):308-316.

39. Korth M, Horn F, Storck B, Jonas JB. Spatial and spatiotemporal contrast sensitivity of normal and glaucoma eyes. *Graefes Arch Clin Exp Ophthalmol.* 1989;227(5):428-435.